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EXAMINER

KIM, YOUNG J

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/057,552

Applicant(s)

MAYO ET AL.

Examiner

Young J. Kim

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-32 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 2-32 is/are rejected.
- 7) ☒ Claim(s) 4-20 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f):
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Claim Objections

Claims 4-20 are objected to because of the following informalities: the claims are drawn to (or dependent on) a canceled claim, claim 1. Appropriate correction is required.

Claims 12, 15, and 16 are objected to because the additional method steps are out of order. For example, claim 12 recites an additional sub-step (D), but its parent claim 2 already recites a sub-step (D). Amending the claim to recite the additional sub-step as (E) would overcome this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite for the recitation of the phrase, "a known protein," because it becomes indefinite at which time and to whom the protein is considered to be known.

Claims 2-20 recite the limitation, "said protein." There is insufficient antecedent basis for this limitation in the claim. Amending the claims to recite, "said protein backbone structure," would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17-20 are product-by-process claims drawn to an optimized protein made by the method claims, a nucleic acid sequence encoding the optimized protein, an expression vector comprising the nucleic acid, and a host cell comprising the nucleic acid.

Claim 21 is drawn to any protein having a sequence that is at least about 5% different from any naturally occurring protein which is at least 20% more stable.

MPEP states that:

“A biomolecule sequence described by only a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence” (MPEP 2163(a)).

The specification discloses a few protein sequences (Gβ1, FSD-1) and their optimization. However, the claims are drawn to any and every protein derived from the claimed process. The claims fail to disclose a correlation between the function and the structure of a reasonable number of the naturally occurring proteins embraced by the genus, the nucleic acids encoding the proteins, a vector comprising the nucleic acids, etc. Further, there is no basis on which to search

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for what is being claimed. Because Applicants have not disclosed a sufficient number of species within the genus to which the claims are drawn, the claims lack in their written description as required under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardman (U.S. Patent No. 4,939,666, issued July 3, 1990, IDS ref # A1).

Claim 21 is drawn to a protein sequence that is at least about 5% different from a known protein sequence that is at least 20% more stable than a naturally occurring protein sequence.

Claims 22-26 are drawn to a computer readable memory that comprises a side chain module to correlate a group of potential rotamers (or residues) for residue positions of a protein backbone and ranking module that analyzes the interaction of each of the rotamers with all or part of the remainder of the protein to generate a set of optimized protein sequences. Some embodiments are drawn to the analyzer module comprising van der Waals, atomic solvation, hydrogen bonding, or secondary structure scoring functions.

Hardman discloses a computerized method/algorithm that determines/predicts a protein's three-dimensional structure (Abstract, column 2). Hardman discloses that the properties of protein depend directly from the protein's three-dimensional conformation and this conformation determines the activity or ability of enzymes, the capacity and specificity of binding proteins,

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and the structural attributes of receptor molecules, recognizing the need in the art for the means to stabilize a protein's three-dimensional structure (column 2, lines 1-9).

Hardman discloses the method process that each residue in consideration must be globally optimized (minimization of total energy, column 10, lines 32-33) as well (column 12, lines 1-12, column 15, lines 50-68) wherein each of the peptide block (or residue in question, or potential rotamer), must be examined for at least several target parameters. Such parameters are disclosed as hydrogen bonding (claim limitation 25, column 38), van der Waals (claim limitation 23, column 39), atomic solvation (or hydration contribution, claim limitation 24, column 39), and entropic contribution/angle-dependent strain, i.e., steric hindrance (or secondary structure of claim 26, column 39).

Hardman also contemplates the substitution of residues in the existing structure to further optimize the structure (column 19, lines 1-22).

Hardman conducts the disclosed method through an algorithm on a computer, necessarily requiring a computer readable memory as evidenced throughout the disclosure.

Finally, Hardman discloses the production of the polypeptide produced by this method which would necessarily allow the generation of the claimed polypeptide.

According to *In re Best* 195 USPQ 430, 1997, the court stated that, "Patent Office can require applicant to prove that prior art products do not necessarily or inherently possess characteristics of his claimed product wherein claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes; burden of proof is on applicant" (pp. 430). Absent evidence that the disclosed method of Hardman

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cannot produce the polypeptide of the claimed, the method of Hardman and the polypeptide produced from said method would inherently anticipate the claimed polypeptide.

Therefore, Hardman anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hardman (U.S. Patent No. 4,939,666, issued July 3, 1990, IDS ref # A1) in view of Lee et al. (U.S. Patent No. 5,241,470, issued August 31, 1993, IDS ref # A2).

Claim 29 is dependent on claim 22, further comprising an embodiment drawn to a computer readable memory further comprising an assessment module to assess the correspondence between the potential energy test results and theoretical potential energy data.

Hardman discloses a computerized method/algorithm that determines/predicts a protein's three-dimensional structure (Abstract, column 2). Hardman discloses that the properties of protein depend directly from the protein's three-dimensional conformation and this conformation determines the activity or ability of enzymes, the capacity and specificity of binding proteins, and the structural attributes of receptor molecules, recognizing the need in the art for the means to stabilize a protein's three-dimensional structure (column 2, lines 1-9).

Hardman discloses the method process that each residue in consideration must be globally optimized (minimization of total energy, column 10, lines 32-33) as well (column 12, lines 1-12, column 15, lines 50-68) wherein each of the peptide block (or residue in question, or potential rotamer), must be examined for at least several target parameters. Such parameters are disclosed as hydrogen bonding (claim limitation 25, column 38), van der Waals (claim limitation 23, column 39), atomic solvation (or hydration contribution, claim limitation 24, column 39), and entropic contribution/angle-dependent strain, i.e., steric hindrance (or secondary structure of claim 26, column 39).

Hardman also contemplates the substitution of residues in the existing structure to further optimize the structure (column 19, lines 1-22).

Hardman conducts the disclosed method through an algorithm on a computer, necessarily requiring a computer readable memory as evidenced throughout the disclosure.

Hardman does not disclose the comparison of the theoretical energy to the energy from the test data.

Lee et al. disclose a method of determining the packing conformation of amino acid side chains on a fixed peptide backbone wherein the side chains are "rotated" (thus rotamers) such that the side chains preferably settle in a low energy packing conformation (thus optimization) (Abstract, column 2, lines 1-25). Lee et al. also disclose that the conformation of energy of a peptide can be modified in many ways, ranging from potential energy functions having van der Waals, torsional biasing, electrostatic interactions, hydrogen bonding, hydrophobic interactions, entropic destabilization, cysteine bond formation, etc. (column 10, lines 54-61).

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Lee et al. disclose that in order to test the reliability and consistency of the method, seven predictions for one protein was made and each of these predictions were compared to that of the native structure (column 25, line 68 to column 26, line 24).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hardman and Lee et al. to arrive at the invention as claimed. One of ordinary skill in the art would have been motivated to combine the teachings because by doing so, one of ordinary skill in the art would have been able to test the accuracy of the three-dimensional protein structure prediction as produced by Hardman. As the methods of Lee et al. and Hardman are directed in the art of protein structure prediction and optimization via computerized algorithm, one of ordinary skill in the art would have had a reasonable expectation of success at combining the accuracy/reliability step of Lee et al. into the method of Hardman to arrive at the invention as claimed.

Therefore, the invention as claimed is obvious over the cited references.

Double Patenting

Applicant is advised that should claim 29 be found allowable, claim 31 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. The method of claim 31 is identical to that of claim 29 with the additional sub-step of "identifying residues in at least one of said optimized protein sequences that differ from the starting backbone." However, addition of this phrase in claim 31 does not make the claim indistinct from claim 29. Claim 29 is already drawn to a method of optimizing a protein structure via rotamer analysis (which involves substituting the rotamers at various places), arriving at a protein sequence which is different than

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the originally input sequence. Although such step is not explicitly recited, one skilled in the art would recognize that such step is implicit. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-20, 30, and 32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37, 39-48, 29, and 32 of copending Application No. 09/837,886. Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth below.

Preliminarily, claims 3-20 of the instant application are verbatim (and identical in scope) to claims 30-37 and 39-48 of the '886 application. Since claims 3-20 of the instant application is dependent on the independent claim 2, and claims 30-37 and 39-48 of the '886 application is dependent on the independent claim 29, the rejection will be drawn to these independent claims only.

The difference between claim 2 of the instant application and claim 29 of the '886 application is in the use of the term "rotamers," used in the instant application versus the term, "amino acids" used in the '886 application. A section of the specification states that, "each amino acid can be represented by a discrete set of all allowed conformers of each side chain, called rotamers" (page 6, top paragraph). In other words, the amino acids are represented by "rotamers." The specification of the '886 application adds that, "[t]hus, to arrive at an optimal sequence for a backbone, all possible sequences of rotamers must be screened, where each backbone position can be occupied by either each amino acid in all its possible rotameric states, or a subset of amino acids, and **thus a subset of rotamers** (page 6, lines 1-5). The specification discloses no other "species" which would represent the "genus" of attributes of amino acids, other than the species of rotamers.

The current situation is analogous to that which was described in *In re Vogel* (164 USPQ 619, CCPA, 1970), wherein the court stated that:

"The correctness of this conclusion is demonstrated by observing that claim 10, by reciting 'meat' includes 'port.' Its allowance for a full term would therefore extend the time of monopoly as to the pork process" (623).

In a similar manner, the present claims drawn to using the rotamers would include the method of using the amino acids of '866 application, rendering the claims obvious over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 2-16, 28, 29, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-15 of U.S. Patent No. 6,188,965 (issued February 31, 2001). Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth below.

Preliminarily, claims 3-16 of the instant application is verbatim to claims 3-15 of the '965 patent. Since claims 3-16 of the instant application is dependent on the independent claim 2, and claims 3-15 of the '965 patent is dependent on the independent claim 2, the rejection will be drawn to these independent claims only.

Claim 2 of the '965 patent is drawn to a computerized method of optimizing a protein structure via rotamer involving at least one scoring function. Claim 2 of the instant application has all of the limitation of the '965 patent claim 2. While claim 2 of the instant application leaves out the phrase, "a set of protein sequences optimized for at least one scoring function," as recited in claim 2 of the '965 patent, the exclusion of such phrase does not make the claim unobvious over claim 2 of the '965 patent because sub-step (D) of claim 2 of the instant application requires that a protein be optimized for steric hindrance (i.e., analyzing the interaction of rotamers with the protein backbone), which is considered to be a scoring function.

The difference between claims 28, 29, and 31 of the instant application and claim 6 of the '965 patent in their analysis step which involves a "forcefield calculation." According to the specification, the forcefield calculation is a part of scoring function (page 37, lines 10-20), more specifically, hydrogen bond scoring function (page 39). The specification discloses no other

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“species” which would represent the “genus” of attributes of hydrogen bond scoring function, other than the species of forcefield calculation as claimed in the present application.

The current situation is analogous to that which was described in *In re Vogel* (164 USPQ 619, CCPA, 1970), wherein the court stated that:

“The correctness of this conclusion is demonstrated by observing that claim 10, by reciting ‘meat’ includes ‘port.’ Its allowance for a full term would therefore extend the time of monopoly as to the pork process” (623).

In a similar manner, the claims involving hydrogen scoring function would include the method of involving forcefield calculation, thereby extending the time of monopoly to the method of using the hydrogen scoring function.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (703) 308-9348. The Examiner can normally be reached from 8:30 a.m. to 7:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (703)-308-3905. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (703) 308-1119. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so


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as to avoid the processing of duplicate papers in the Office. The Fax number is (703) 746-3172. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Young J. Kim

7/7/03




JEFFREY SIEW
PRIMARY EXAMINER

7/11/03